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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	19

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
09/132,521	NAGAI ET AL
Examiner	**Art Unit**
Joseph Woitach	1632

Office Action Summary

-- The *MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Peri[o]d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on _____.

2a) This action is **FINAL**. 2b) ☐ This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) *1-12, 14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) *1-12, 14 and 15* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 18
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph Woitach** and the group art unit is now **1632**.

This application is an original application filed August 11, 1998. Applicants response to the previous office action has been received and entered (paper 17). Claims 1-12, 14 and 15 are pending and currently under examination

Response to Amendment

Three declarations have been filed under 37 CFR 1.132, one by Yoshiyuki Nagai, an inventor on the instant application, one by Yasuji Ueda and one by Markoto Inoue, both research scientists at DNAVEC, the assignee of the instant application (attachment to paper number 17).

The declaration of Yoshiyuki Nagai filed under 37 CFR 1.132 filed March 16, 2001 is sufficient to overcome the rejection of claims 1-8, 11, 12, 14 and 15 based upon the Moriya *et al.* reference applied under 35 USC 102(a). The declaration indicates that the authors Tatsuo Shioda and Chikaya Moriya, in addition to Yoshiuki Nagai, are co-inventors on the instant application and responsible for the subject matter disclosed therein. Further, each of the remaining authors contribution to the reference of Moriya *et al.* is detailed, and the declaration indicates that the

work related to the instant application was performed under the direction and supervision of Yoshiuki Nagai.

The declaration of Markoto Inoue filed under 37 CFR 1.132 filed March 16, 2001 is insufficient to overcome the rejection of claims 1-8, 11, 12, 14 and 15 based upon the combination of Yu *et al.* and Bleul *et al.* applied under 35 USC 103(a) as set forth in the last Office action because: the data presented and arguments suggesting that protein expression is unpredictable are not found persuasive. The declaration will be discussed in detail below.

The declaration of Yasuji Ueda under 37 CFR 1.132 filed March 16, 2001 is insufficient to overcome the rejection of claims 9, 10, 11, 12 and 15 based upon insufficiency of the disclosure under 35 USC 112, first paragraph as set forth in the last Office action because: the *in vitro* data presented and arguments presented do not provide a nexus between the art recognized obstacles of gene therapy as set forth in the previous office action for one of skill in the art to practice the invention as claimed. The declaration will be discussed in detail below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

Claim 9, 10, 11, 12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that the basis of the present rejection is directed to the method of treating HIV infection in a human (claims 9 and 15) and the claimed pharmaceutical compositions (claims 10, 11 and 12) as they would be used in said method. The use of the compositions and methods for *in vitro* use encompassed by claims 11, 12 and 15 are the basis of the 35 USC 103 rejection below.

Applicants argue that the specification plainly teaches *in vivo* and *ex vivo* gene therapy methods, and point the specification page 8, lines 36-37 and for specific dosages page 9, lines 1-4. In addition, Applicants point to a newly cited reference Yonemitsu *et al.* (2000) demonstrating that lung epithelial cell can be infected with Sendai virus and express luciferase, and the declaration of Dr. Ueda indicating that Sendai virus vectors can be used to infect CD34 positive cells *in vitro*, to support the use of Sendai virus in gene therapy protocols. Applicants argue that a skilled medical practitioner is capable of determining the appropriate dosage of a Sendai virus. Further, Applicants point out that to satisfy enablement requirement of 112, first paragraph, one only need demonstrate pharmacological activity *in vitro* citing *In re Brana* and MPEP 2107.02 in support of their argument. See Applicants amendment pages 2-7. Applicants arguments have been fully considered but not found persuasive.

First, Examiner would concede that one of ordinary skill in the art could use a Sendai virus vector to infect cells *in vivo* and obtain expression of a polynucleotide in said cell, however

the basis of the rejection is not if this can simply be done, it is rather has the specification provided the necessary guidance to practice the method and to provide a therapeutic affect. Examiner does not dispute that CD34 cells can be infected *in vitro* as illustrated by the declaration of Dr. Ueda or as demonstrated by Yonemitsu *et al.* that cells can be infected *in vivo* and express a marker gene. As set forth in the previous office action, the specification pointed to by Applicant provides only variables or modifications that the one of ordinary skill in the art must consider. There is no indication in the specification what levels of what chemokines would be therapeutic *in vivo*, nor that such a therapeutic level could be attained using the Sendai virus vector, nor that the levels expressed *in vitro* can be correlated to levels of protein expression which can be attained *in vivo*. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). With respect to the instant invention, as noted in the declaration of Dr. Inoue the level of expression of a vector protein cannot be predicted beforehand (declaration by Dr Inoue, paragraph 10). Applicants face the same shortcomings faced by others skilled in the art with regards to the specificity of cell targeting and the ability to regulate gene expression. Large levels of expression of gene of interest are not all that is necessary to enable methods of gene therapy, and as pointed out in Applicants own arguments, it can actually be deleterious due to aggregation and loss of function of the expressed protein. Besides the general expectation that it will require years of further research to develop effective gene therapy (Verma *et al.*), it would require extensive research to understand the fundamental biology of the system to which the claimed methods apply. The level of skill in molecular biology is high, however the necessary guidance to

overcome the art recognized obstacles must be taught to provide an enabling disclosure. Verma *et al.* summarize " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged," and conclude that the problems, such as lack of efficient delivery systems, lack of proper expression, and host immune response reactions remain formidable challenges. Examiner agrees with Applicant that working *in vivo* examples are not necessary given the necessary *in vitro* evidence (*In re Brana* and MPEP2107), however Applicants have failed to provide a nexus between the results achieved *in vitro* and predictable success *in vivo*.

Therefore, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and the state of the art at the time of the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed, and thus the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-8, 11, 12, 14 and 15 rejected under 35 U.S.C. 102(a) as being anticipated by Moriya *et al.* is withdrawn. The declaration of Yoshiyuki Nagai filed under 37 CFR 1.132 is sufficient to overcome the rejection of record because in view of the declaration the Moriya *et al.* reference does not constitute prior art (*In re Katz*, 687 F.2d 450 (CCPA 1982)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11, 12, 14 and 15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yu *et al.* and Bleul *et al.*

Applicants summarize the claimed invention and the teachings of both references. Applicants argue that in light of Yu's failure to produce an active luciferase in an eukaryotic system, that one of skill in the art would not have been motivated to use the Sendai virus vector system to express a chemokine. Further, it is argued that the successful expression of gp120

using a Sendai virus vector cannot be extrapolated to all proteins. In support of this argument, Applicants have supplied a declaration by D. Makoto Inoue demonstrating that NGF and GDNF are not produced to the same level in cells infected with the same amount of Sendai virus. Dr. Inoue concludes "that all though the exogenous gene has no influence on the replication of the Sendai virus itself, it influences the production efficiency of the proteins when using a Sendai virus vector, to an extent that the effect of the vector-protein combination cannot be predicted beforehand" (page 2, last line in paragraph 10 of the Inoue declaration). In addition, with respect to the Bleul reference, Applicants argue that Bleul *et al.* do not suggest using a Sendai virus to produce a chemokine. See Applicants amendment pages 8-12. It is concluded that light of the teachings of the two references that the claimed 'invention succeeded where other had failed" and that there is nothing in either reference to suggest the claimed invention would be successful and that they do not convey a reasonable expectation of success. See applicants amendment pages 13-14, bridging paragraph. Applicants arguments and declaration have been fully considered but not found persuasive.

First, with regard to the declaration of Dr. Inoue, the declaration lacks the details necessary to fully evaluate the data presented. It is unclear how the amount of each of the factors were quantified and the similarities or differences of the vectors and cells used for each of the factors. Given that all variables in the experiments performed were equal except for the coding sequence of the polynucleotide that was introduced into the Sendai vector, Examiner would agree that the data presented indicates that different polynucleotide sequences will produce proteins at

different levels. However, this fact is well recognized by one of ordinary skill in the art. This is illustrated in part by the data presented in Table 1 of Yu et al. showing that different cell types produce various amounts of protein when the same expression Sendai vector is used. Further, there is no indication from the data that either of these amounts of protein produced is not or would not be considered 'a substantial amount' nor that the proteins are or are not biologically active. Finally, the data supports that two unrelated sequences can be expressed. In conclusion, there is nothing in the declaration that would lead one to conclude that a polynucleotide encoding any polypeptide would not be expressed when inserted in a Sendai virus vector system.

Secondly, with respect to the Yu *et al.* reference, the reference clearly indicates that gp120 can be expressed by various cell types albeit at various levels (see for example page 460; Table 1). Applicants arguments center on the fact that a biologically active form of luciferase was not produced and that one of ordinary skill in the art would not expect other proteins to be successfully produced. It is noted that Applicants point out that the art teaches that chemokines are prone to aggregation, however the portions of the specification pointed to by Applicant only indicate that 'chemokines are produced in *E. coli* with low productivity' (page 2; third paragraph) not that chemokines cannot be produced. In addition, a quick search of the art indicates that several chemokine molecules were cloned and expressed in mammalian systems prior to the filing date of the instant application. For example, in the newly cited reference of Czaplewski *et al.*, the authors summarize the structure of various chemokines and indicate that '[N]ot all chemokines self-associate' (page 16078; top of first column). In addition, Examiner agrees with Applicants

arguments that aggregation depends on various external factors such as temperature and protein concentration (Applicants amendment page 10) and notes that luciferase protein was produced by Yu *et al.* even though the protein formed an aggregate. In light of the fact that chemokines had been successfully produced prior to the filing of the instant application, that aggregation of a protein is an effect of external factors, and that Sendai virus had been used successfully to express proteins in various cell types, Applicants arguments that one of ordinary skill in the art would not have expected to be able to express a chemokine using a Sendai virus vector is unpersuasive.

Finally, with respect to Bleul *et al.* reference, it is noted that Bleul *et al.* do use a synthetic chemokine, however, it is also taught that SDF-1 had already been cloned and characterized (page 830; top of first column). In light of the general teaching of Yu *et al.* teaching that Sendai virus has realistic utility and broad application in to express large amounts of a protein and the specific teaching evaluating the effect of HIV infection, and the specific teaching of Bleul *et al.* that SDF-1 blocks HIV entry, as noted in the previous office action, it would have been obvious to one of ordinary skill in the art to combine the teachings to evaluate the effect of chemokines in various cell types. As detailed above, there would have been a reasonable expectation of success by one of ordinary skill in the art to express a chemokine using a Sendai virus vector.

Therefore, for the reasons above and of record, the invention is *prima facie* obvious, and the rejection is maintained.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Joseph T. Woitach

JILL D. MARTIN
PRIMARY EXAMINER

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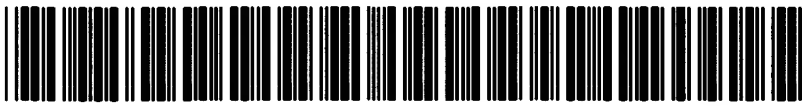

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